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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
EWOLDT, G	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/382,837	Applicant(s) Borodic, G.E.
	Examiner G. R. Ewoldt	Art Unit 1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *4/30/01 and 5/16/01*.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above, claim(s) *9 and 13-16* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-8, 10-12, and 17-23* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *2, 9*

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

1. Applicant's election with traverse of Group I, claims 1-8, in Paper No. 7, filed 5/16/01, is acknowledged. Applicant argues that Groups I-IV and VI are technically related, thus the search of all together would pose no undue search burden.

These argument are not found persuasive for the following reasons. While Groups I, III, and IV encompass methods of treatment for related inflammatory disorders, Groups II and IV encompass methods comprising significantly different fields of search. The invention of Group II encompasses the blocking of mast cell degranulation which, while possibly overlapping, is not coextensive with a method of treating inflammatory disorders. Group IV encompasses the treatment of photophobia which is not necessarily an inflammatory disorder. Upon further consideration, however, Groups III and IV have been rejoined with Group I.

The requirement is still deemed proper and is therefore made FINAL.

2. Claim 9 and 13-16 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

Claims 1-8, 10-12, and newly added claims 17-23 read on the elected invention and are being acted upon.

3. The declaration is objected to because it claims priority to Provisional Application No. 60/097,864. Applicant presumably intends to claim priority to Provisional Application No. 60/097,846 as indicated in the first line of the specification. A new declaration is required.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 2-8, 12, and 18-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

A) in claim 2, the term "substantial" muscle weakness has not been defined, thus, the metes and bounds of the claim are indefinite. Note that in the instant context muscle weakness has

not been defined, thus, said weakness might range from the undetectable to total paralysis. As such, "substantial" weakness is impossible to define,

B) in claims 3, 5, and 6, "the" chemodenervating agent is properly "said" chemodenervating agent,

C) in claim 4, "units" has not been defined, thus, the metes and bounds of the claim are indefinite. The specification discloses "units", "mouse units", and "LD 50 units", none of which are specifically defined in the specification, thus, the metes and bounds of the claim are indefinite,

D) in claim 6, the term "used" is vague and indefinite. The term "administered" is suggested, further "other anti-inflammatory agents" is properly "an other anti-inflammatory agent",

E) in claims 7-8, "the" other agent is properly "said" other agent,

F) in claim 12, "the" hypersensitivity is properly "said" hypersensitivity,

G) in claims 18 and 20, "the" botulinum toxin is properly "said" botulinum toxin,

H) in claims 19 and 21-23, "the" neurogenic inflammation is properly "said" neurogenic inflammation.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 17-23 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection. Note that claims 17-23 wew submitted in a preliminary amendment, filed 5/16/01, and are not part of the application as originally filed on 8/25/99. Thus, said claims comprise new matter added after the original filing of the application.

The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically:

A) "a method for treating neurogenic inflammation" and "at least one neurogenic inflammatory mediator" (Claims 17, 19, and 21-23),

B) "substance-P, calcitonin gene-related peptide, vasoactive intestinal peptide, interleukin-1, interleukin-2, nitric oxide, 5-hydroxytryptamine, tumor necrosis factor, and nerve growth factor," (Claim 19),

C) "wherein the botulinum toxin is less than about or equal to 1000 U" (Claim 20),

D) "wherein the neurogenic inflammation is caused by gout" (Claim 22),

E) "treating the neurogenic inflammation by inhibiting histamine" (Claim 23).

Applicant's amendment, filed 5/16/01, assert that support can be found for the new claims in the specification. However, no specific passages have been found in the specification reciting the newly claimed limitations.

8. Claims 2-5 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

a method of reducing allergy induced conjunctivitis in a mouse by injecting 0.675 mouse units of botulinum toxin type A, does not reasonably provide enablement for:

A) a method of reducing inflammation without causing substantial muscle weakness,

B) a method of reducing inflammation comprising an effective dose of botulinum toxin less that 2.5 units,

C) a method of reducing inflammation comprising administering botulinum toxins B-G.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation. The scope of the claims is not commensurate with the enablement provided by the disclosure.

Regarding A and B, the critical element of the claim is the extremely low dose of the toxin that might still retain anti-inflammatory effects. The specification, however, discloses only one rat example (CONJUNCTIVITIS) in which the toxin is used at such a low dosage. It is noted that in all the human examples the toxin is used in at least a dosage of 2.5 units. Additionally, in each human example, the toxin is used at a dosage specifically intended to cause muscle weakness and the anti-inflammatory properties are merely observed as a side effect (see particularly Case I and Case II. As such, the claim to a method employing an effective dose of botulinum toxin less that 2.5 units is mere assertion, said assertion being highly unpredictable as the method is not recognized in the art as a

method of reducing inflammation (see The Merck Manual, 1992, pages 318-320). Said method would require significant enablement, i.e., working examples, given said unpredictability.

Regarding C, Borodic et al. (*Neurology*, 1996, IDS) teaches that different botulinum toxin subtypes possess significantly different therapeutic properties and require administration at significantly different concentrations. Given these known differences, the administration of botulinum toxins about which little is known would be highly unpredictable. Claims reciting said administration would require significant enablement, i.e., working examples, given said unpredictability.

In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Thus, in view of the quantity of experimentation necessary, the lack of sufficient working examples, the unpredictability of the art, and the lack of sufficient guidance in the specification regarding both how to both make and use the claimed invention, it would take undue trials and errors to practice the claimed invention.

9. The instant application claims the benefit of priority to Provisional Application No. 60/097,864. Applicant presumably intends to claim priority to Provisional Application No. 60/097,846. Claims 1 and 5-8 are granted said benefit of priority. However, the '846 application does not disclose the use of a chemodenervation agent at doses sufficient to reduce inflammation but insufficient to cause substantial muscle weakness. Neither does the '846 application teach a method for treating neurogenic inflammation. Accordingly, Claims 2-4 and 17-23 are denied the benefit of priority. The priority date of said claims is the filing date of the instant application, 8/25/99.

10. Applicant's request that an interference be declared between the instant application and U.S. Patent No. 6,063,768 is acknowledged. However, no interference shall be established until such time as all pending claims are found allowable **and** Applicant has submitted appropriate evidence showing entitlement to said declaration.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 3© of this title before the invention thereof by the applicant for patent.

12. Claims 1 and 5 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by U.S. Patent No. 6,159,944 (filed 2/27/98).

The '944 patent teaches a method of reducing inflammation (anal fissures) comprising administering a botulinum toxin chemodenervating agent to an anatomic region (see particularly column 1, lines 25-33). Note that the use of type A botulinum toxin would be inherent as type A was the only botulinum toxin approved for use in the United States at the time of the invention.

The reference clearly anticipates the claimed invention.

13. Claims 1, 5-6, and 17-23 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,063,768 (filed 9/04/97)

The '768 patent teaches a method of reducing neurogenic inflammation by inhibiting at least one neurogenic inflammatory mediator (such as substance-P) by interrupting a neurogenic pathway, comprising administering a botulinum toxin type A chemodenervating agent to an anatomic region in a dose of 5 LD 50 units or at a dose of 1000 units, in conjunction with other anti-inflammatory agents (inflammatory antagonists). Further, the reference teaches the treatment of inflammatory disorders including rheumatoid arthritis and gout, and the inhibition of histamine (see particularly column 2, lines 34-60, columns 5-7, and Claims 1-6).

The reference clearly anticipates the claimed invention.

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. Claims 1, 5-8, 10-12, and 17-23 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,063,768 (filed 9/04/97)) in view of The Merck Manual (1992).

The '768 patent has been discussed above.

The '768 patent differs from the claimed invention in that it does not teach a method of reducing inflammation due to blepharoconjunctivitis, hay fever, rhinitis, or type 1 hypersensitivity. Neither does the '768 patent teach the use of other anti-inflammatory agents comprising steroids or non-steroids.

The Merck Manual teaches that blepharoconjunctivitis, hay fever, rhinitis, and type 1 hypersensitivity are inflammatory disorders amenable to treatment by anti-inflammatory agents (see particularly pages 318-320 and 2368). The reference further teaches that steroidal and non-steroidal drugs are common anti-inflammatory agents (see particularly pages 1308-1311).

From the teachings of the references it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to perform a method of reducing neurogenic inflammation by inhibiting at least one neurogenic inflammatory mediator comprising administering a botulinum toxin type A chemodenervating agent to an anatomic region, in conjunction with other anti-inflammatory agents, as taught by the '768 patent, substituting a steroidal and non-steroidal drug as the specific additional anti-inflammatory agent, as taught by The Merck Manual for the treatment of inflammatory conditions such as blepharoconjunctivitis, hay fever, rhinitis, and type 1 hypersensitivity, as taught by The Merck Manual. One of ordinary skill in the art would have been motivated to make said substitutions because blepharoconjunctivitis, hay fever, rhinitis, and type 1 hypersensitivity are inflammatory disorders amenable to treatment by anti-inflammatory agents, as taught by The Merck Manual, and steroidal and non-steroidal drugs are common anti-inflammatory agents, also taught by The Merck Manual.

16. No claim is allowed.

17. The references on the on the form PTO-1449, filed 5/16/01, have been numbered for ease of identification. References 8, 29, 53, 65, 82, and 83 have been lined through and have not been considered because they have not been provided. Reference 12 has not been considered because its source has not been identified. Reference 81 has not been considered because the year of its publication has not been identified. References 68-80 have been provided, and thus considered, as abstracts only.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (703) 308-9805 The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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